ADVANCE DEVELOPMENT AND CURRENT CHALLENGE IN NAIL DRUG DELIVERY

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ABSTRACT

Onychomycosis is a very common nail disease. It may be caused by dermatophytes, yeast, and nondermatophyte fungi. Traditionally, oral antifungal medications have been used to treat fungus, although they may be associated with side effects and drug interactions. Topical treatment provides an alternative, to bypass the effects of the oral medication system; Recent research has focused on drug development and development. Physical therapy and laser are used in conjunction with topical, which can help penetrate the nail plate. In this review, strategies from all categories are clarified: both novel and experimental evaluation methods and the effectiveness of newly developed therapies. More long-term research is needed to determine the effectiveness of various therapies, but treatment levels are improved as patients adhere to treatment and follow preventative measures to avoid recurrence.

KEYWORDS: Onychomycosis, Tineapedis, Dermatophyte, Toenail, Disease, Antifungal, Laser.

1. INTRODUCTION

The nail unit is a major part of the cutaneous musculo-skeletal appendage. Treatment of nail problems is a difficult task due to the manifestation of the disease and the anatomical structure of the nail plate. Treatment of headaches / nail disorders has been the center of nail
research for the past few decades as it offers a more secure and focused alternative to conventional oral treatment. However, transungual delivery had its challenges. This necessitates the consideration of new approaches that improve the effectiveness of treatment and reduce the duration of treatment. In addition, healing the condition of the nails using the submission of articles has been a challenge due to the lack of a proven animal model to determine the efficiency of the structure and to establish a mathematical model that can help predict desirable properties for the formation and penetration of various molecules.

The purpose of this review is to provide a summary of nail anatomy and its disorders, features affecting nail delivery, diagnostic procedures, current methods, and promising treatments for nail disease / disorders including nail lacquers and the role of permeation enhancers, in-vitro. models. These reviews include currently available treatments and treatments under clinical evaluation.

Onychomycosis is a fungal infection that occurs in the nails and may affect the surrounding skin. In general, it appears to be a change in nail color, hardening of the nail plate, and onycholysis.\textsuperscript{[1]}

It is the most common nail pathology and accounts for about 90% of toenail infections worldwide. Including local pain, paresthesia, and reduced quality of life as its appearance may interfere with social interaction and daily activities.\textsuperscript{[2]} Most onychomycoses are caused by the dermatophyte Trichophyton, Trichophytonrubrum, Trichophytonmentagrophytes, and Epidermophyton.\textsuperscript{[3]} Infections usually begin with tineapedis, fungal infections of the surrounding skin of the feet.\textsuperscript{[3]} Factors that contribute to the progression of the disease moisture, occlusive shoes, nail polish, and genetic predisposition\textsuperscript{[4,5]} Patients with diabetes, vascular dysfunction, HIV, and a weakened immune system are at greater risk, as do older patients.

Due to the chemical composition, the nail is a formidable barrier to drug entry, and the spread of the nails is much worse compared to the skin. Well until a healthy nail has regenerated. Traditionally, oral medications have been the preferred treatment due to their accessibility and effectiveness. Terbinafine and itraconazole US Food and Drug Administration (FDA) - an oral medication that fights fungal, and fluconazole is available as a non-label option in the US. Although they work well, they may be associated with systemic side effects and drug interactions, which worries those who are already taking certain medications. Patients may be reluctant to take oral antifungals. Understandably, there is a need for non-systemic treatment.
Currently, there are several types of oral, topical, and physical therapies that extend the range of treatment available to patients. Additionally, a combination therapy with a few classes/drug modes can be considered as other research teams are researching new molecules and permeation enhancements for topics, various drug targets, and improving the efficiency of existing molecules. When the effectiveness of these drugs is measured, the outcome measures commonly used are mycological treatments and holistic therapies. Mycological treatment is defined as the eradication of a fungal pathogen from the nail, which is confirmed by the correction of negative potassium hydroxide (KOH) (tests to distinguish dermatophytes and yeasts from other skin diseases) and a fatal fungal culture. Comprehensive treatment meets the goals of the patient, physician, and control bodies. Complete treatment is defined as 100% clear nail polish (also known as clinical treatment) in addition to mycological treatment. This review will highlight some of the latest developments in onychomycosis control.

2. Major challenge

The nail surface or plates are strong and durable due to the stable disulphide bonds that will be limited to drug penetration into the nails. Permeate texture applied to the side of the male bar.[6]

It is important to consider the physicochemical properties of the drug cell, the composition components, the potential interaction between the drug and keratin and the potential penetration enhancement when designing nail structure.

In oral antifungal treatment, liver function tests should be performed regularly. Such drugs are expensive and disruptive even due to the patient's poor adherence. So topical treatment is always an option in maternity plan.[7]

3. Transungual drug delivery

Transungual drug delivery is defined as a program related to drug trafficking across the nails to provide targeted drug delivery to treat nail infections. In the word transungual, "Trans" means "with" and "unguis" means "nails".[8] The Transungual drug transport system is thought to be very effective in controlling nail disorders due to its better adhesion, local action, which provides adverse effects on the small system.[9] Unconventional therapies offer some advantages over oral / prescribed drugs in such a way that preparation is relatively easy compared to oral dosage forms such as pills, etc. Drug interactions and systemic side effects are non-existent. Local side effects associated with abnormal eruptions such as periungual
erythema of the proximal nail fold gradually disappear after a few minutes and usually subside over time as the body adapts to the new drug. The formal absorption is minimal and is based on subject use a structure that can be easily removed if needed. Unauthorized treatment provides improved adherence and is suitable for those who are unable to take system medication. It is best if older patients and patients receive multiple doses to avoid drug interactions. Despite having several benefits, it also causes various problems such as nail plate formation, drug penetration restrictions, and allows a small portion of the topical drug to penetrate beyond and that is why the focus of the desired treatment will not be achieved.\cite{11}

4. Transungual drug delivery methods
Nail penetration can be achieved in a variety of ways such as mechanical, chemical (maturation enhancement), and physiological methods (such as iontophoresis, microneedles, etc.) as discussed in the previous text and highlighted in Figure 1.
Skin As a Barrier to Transdermal Drug Delivery

The skin is the most important organ and the largest organ comprising the three main layers (epidermis, dermis, and hypodermis) (Hendriks et al., 2006). It forms a range of important functions, such as defense (biological, mechanical, chemical, and physical) and hydro and thermo-regulation (Roosterman et al., 2006). The skin appears to be the central route of drug delivery by allowing the regulated drug to travel through the stratum corneum (SC) to additional areas within the skin, which may contribute to systemic proliferation (Sala et al., 2018). Its wide range improves drug concentration, and thus large amounts of drugs can be effectively distributed through transdermal delivery systems. However, SC skin also prevents the immersion of other types of low-dose and / or heavy-duty drugs (Schroeder et al., 2007; El Maghraby et al., 2008).
The function of the skin barrier is almost completely accomplished and significantly remarkable by the stratum corneum (SC) - a unique biomembrane morphologically and compositionally (Scheuplein and Blank, 1971). This is very thin (about 1/100 mm), a slightly infiltrated skin layer is the final step in the epidermal separation process, forming a laminate of compressed keratin-filled corneocyte embedded in the lipophilic matrix (Christophers, 1971; Elias, 1981, 1983). The lipids of this extracellular matrix differ in many ways (Gray et al., 1982; Williams and Elias, 1987) that is, (i) they provide a unique distribution mechanism and a continuous phase from the skin surface down to the SC; (ii) the structure of the skin is different from biomembranes and most interestingly it does not contain phospholipids; (iii) despite these lipid deficiency, SC lipids produce multilamellar sheets; and (iv) long series, highly hydrocarbon tails provide a structured, integrated and structured gel-based cell membrane contrasts with conventional crystalline membrane systems.

However, it appears that the abnormal lipid matrix alone cannot fully explain the prominent membrane resistance, and the formation of SC as a whole has been suggested to play an important role in skin prevention. Therefore, the arrangement of the moving corneocyte in lipid continuity is suggested to provide a more distorted form of lipoidal diffusion that makes it enter water 1000 times in water compared to other biomembranes (Potts and Francoeur, 1991). The transport role of this twisted pathway is further illustrated by observational studies involving the localization of various intercellular channels (Nemanic and Elias, 1980; Bodde et al., 1991), kinetic analysis of in vivo skin penetration of a variety of different models. (Albery and Hadgraft, 1979), and evidence from thermotropic biophysical studies of the lipid domain (Golden et al., 1987; Potts and Francoeur, 1990). Figure 2 shows a view of the system of different skin layers.

**Routes for drug injuries to the skin**

Various studies have been conducted to determine the penetration of topical compounds into the skin. The penetration of the drug into the skin requires that the stored epidermis must be dispensed. The human skin additionally contains sweat glands and hair follicles, which form the lining of the epidermis, consisting of about 0.1% of the total skin (Illel, 1997). The penetration of the drug into the skin is usually controlled by the stratum corneum. Two different transcellular and intercellular pathways are proposed for drugs to overcome this complete barrier. Tinea Unguis: It also called as ringworm of the nails, is characterized by nail thickening, deformity, and eventually results in nail plate loss.
Diseases to nails

A) Paronychia

These nail fold infections can be caused by a variety of bacteria, fungi and other germs. Folded and lateral nails act as a barrier, or mark, between the nail plate area and the surrounding cells or tissues. The infection will be characterized by pain, redness and swelling of the nails. People who have been immersed in water for a long time may have this condition, and it is highly contagious.\(^{[12]}\)

![Figure 1: Paronychia diseased nail.](image1)

B) Pseudomonas bacterial infection

This may or may not occur between the natural area of the nail or plate and the nail bed, and/or between the artificial nail cover and the natural nail plate. Many people have led them to believe in the old 'green' color change of this type of fungal infection. The color change of the nails will darken, deepening the nail plate/bed layers. If germs get inside or on the nail plate and nail bed, they can cause or cause a similar color change and can also cause the nail.\(^{[13]}\)

![Figure 2: Pseudomonas bacterial infected nail.](image2)
C) Fungal or yeast infection
A fungal infection or yeast that leads to Onychomycosis, can lead to pain in the lining of the adjacent nails and the eponychium. This type of nail infection will be characterized by onycholysis (separation of the nail plate) and transparent debris under the nail plate. As the infection progresses to the organic debris that accumulates under the nail plate it often changes color. Other infectious diseases may be involved, and if left untreated, the nail plate may separate from the nail bed or the top.[14]

![Figure: Fungal or yeast infected nail.](image_url)

D) Tinea unguis
Also called nail polish, it is characterized by stiffness of the nails, deformities, and eventually causes loss of the nail plate.

![Figure: Tinea Unguis diseased nail.](image_url)

E) Onychatrophia
Onychatrophia is a atrophy or damage to the nail plate that causes it to lose its luster, become thinner and sometimes completely disintegrate. Injuries or illnesses can cause this
misbehavior.

![Figure 6: Onychatrophia diseased nail.](image)

F) **Onychogryphosis**

Onychogryphosis is a type of nail polish that is characterized by a thick nail plate and is usually the result of trauma.\(^{[23]}\) This type of nail plate will curve inward, compressing the nail bed and sometimes may require surgical intervention to alleviate the pain.\(^{[15]}\)

![Figure: Onychogryphosis nail.](image)

G) **Onychorrhexis**

Onychorrhexis are fractured nails that often split straight up, peel and / or have straight backs. These abnormalities may be the result of genetics and old-fashioned cleaning solutions. Although oil or paraffin is a strong solvent for Onychogryphosis it is a type of nail polish that is characterized by a thick nail plate and is often the result of trauma.\(^{[23]}\) This type of nail plate will rotate inwards, compressing the nail bed and may sometimes require surgical intervention to alleviate the pain.
Figure: Onychorrhexis diseased nail.

G) Leuconychia
They appear as white lines or dots on the nail plate and may be caused by small air bubbles trapped in the layers of the nail plate due to injury. This condition may be hereditary, and no treatment is needed if the spots are to grow on the nail plate or nail surface.

H) Beau's lines
In this case the nails are marked with horizontal lines of black cells and line pressure. These disorders can be caused by trauma, illness, malnutrition or any major metabolic condition, chemotherapy or any other adverse event, and this is the result of any disruption in the protein formation of the nail plate.

I) Koilonychia
It can often occur or be caused by a lack of iron anemia. These nails show high, narrow and dense ridge. [16]

J) Hematoma
It is a result of the trauma of the nail plate. It can range from grabbing with your finger or toe to the car door to a collision from improper or 'too strong' shoes, to sports-related injuries and a hammer does a good job at causing a hematoma again. The nail bed will bleed as a result of this trauma, and blood will be trapped between the nail bed and the nail plate. A hematoma may lead to fractures. Most people who participate in sports activities have a good knowledge of the hematoma due to the constant conflict that arises from the shoes against the nails. A hematoma may cause the plate plate to break down and become infected because the blood can attract fungi and bacteria28. Once a few days have passed and the blood clot becomes painful, the nail plate may need to be removed in order for the nail bed to be cleaned.
Second onychomycosis - another subtype represents the final stage of progression of all the above subtypes. The name of this subtype is TDO - total dystrophic onychomycosis, which is the second of the four smaller types. TDO may be due to chronic mucocutaneous candidiasis.

K) Onychomycosis

Onychomycosis (Tineaunguium) is a fungal disease of the nails, accounting for 50% of nail infections. It affects about 5% of the world's population. The definition of onychomycosis is derived from the Greek language, i.e. onyx - nail, mykes - fungus. It may include any part of the nail unit, namely the nail plate, the nail bed, and the nail matrix. Onychomycosis is a common, incurable and difficult to eradicate toe and nail fungus that affects 10-30% of people worldwide. Clinically onychomycosis is characterized by changes in color, density, and abnormalities. It deals with about 50% of all nail problems. Risk factors for nail infections are diabetes, age, smoking, immune damage such as HIV and vascular disease.

There are seven subtype clinical patterns of onychomycosis

a) DLSO – Distal and lateral subungual onychomycosis
b) SO – Superficial onychomycosis (white or black)
c) EO – Endonyxonychomycosis
d) PSO – Proximal subungual onychomycosis
e) MPO – Mixed pattern Onychomycosis
f) TDO – Total dystrophic onychomycosis

Current treatment

Antiretroviral therapy involves the treatment of oral infections with antifungals - such as Imidazole, Terbinafine, Griseofulvin etc. However, about 20% of patients — they do not respond to treatment and recurrence is common. Statistics show that 22.2% of patients with onychomycosis treated with Terbinafine or Itraconazole orally experienced recurrence during a 3-year follow-up study. Long-term administration of anti-fungal agents causes liver toxicity. Itraconazole is associated with liver damage; liver function tests are required if treatment exceeds 1 month. Oral therapy also contains large doses of active ingredients that require long-term treatment that reduces patient compliance. In addition the initial pass metabolism and system interaction leaves a small fraction to achieve a local effect. Treatment of nail psoriasis involves the monthly injection of corticosteroids on the edges of the nail (the skin around the nail plate). Such injections are very painful and need to be repeated every month 4-6 times which lead to the patient's discomfort. Therefore, look at the submission of
topics and objectives to overcome all the barriers mentioned above was an hour requirement and indicated the following:[17]

1. **Oral therapy with antifungals:** Imidazole, Terbinafine, Griseofulvin.

2. **Mechanical methods**
   I. Nail Avulsion: Separation of infected nail from surrounding structure surgically using Freer's elevator.
   II. Nail Abrasion: Use of sandpaper for eroding nail plate to decrease its thickness or remove it completely.

3. **Chemical methods**
   I. Nail softening agents: Urea, Salicylic acid.
   II. Keratolytic agents: Tolnaftate, 2-mercaptoethanol, papain, 1, 4-Dithiothreitol.

4. **Surfactants:** SLS, Tween-20, Poloxamer–168.

5. **Keratolytic enzyme:** Keratinase.

6. **Medicated lacquers:** Loceryl®, Penlac®.

7. **Iontophoresis:** Enhance permeation Treat fungal nail disorders.

8. **Ultrasound mediated delivery:** Increase transungual drug flux.

9. **Pulsed lasers:** Disruption of keratin chains of nail plate.

10. **Etching:** Phosphoric acid.

11. **Hydration and Occlusion:** Water as plasticizer.18

**Intercellular lipid route**
The stratum corneum (SC) has interlamellar areas, such as connecting regions, ordered lipids, and stable hydrophobic chains that provide a random gap between both neighboring cells and the crystalline lipid lamellae of the cell wall. For transepidermal distribution of lipid as well amphiphilic particles, the lipids in the skin layer are very important, filling these migration gaps and deposits (Geinoz et al., 2004; Ly and Longo, 2004). Hydrophilic molecules are widely dispersed “side by side” in areas where lamellala gaps are filled with water or certain volumes. White molecules can utilize the gaps located at the same end between the outer layer and the lamella corneocyte (Gupta and Trivedi, 2016).[19]

**CONCLUSION**
Nanotechnology has shown many benefits for the delivery of topical and transdermal drugs. It has been reported with various drugs that topical / transdermal formation associated with NPs can increase skin penetration, increase therapeutic efficacy, target the epidermis or follicles,
and reduce adverse events. Alternatively, improved functions are recorded. Most of these delivery systems can be used for both hydrophilic and lipophilic particles. Continued improvements within structures, processing processes, and processes promote the production of new and improved nanocarriers. Integrated physical therapies and nanocarrier-based drug delivery have seen significant progress in the field of advanced drug delivery. However, future research needs to better establish an integrated system of drugs to be used in nanocarriers and calculate their level of risk.

REFERENCES


